Feature Review

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An excitatory synapse hypothesis of depression

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Depression is a common cause of mortality and morbidity, but the biological bases of the deficits in emotional and cognitive processing remain incompletely understood. Current antidepressant therapies are effective in only some patients and act slowly. Here, we propose an excitatory synapse hypothesis of depression in which chronic stress and genetic susceptibility cause changes in the strength of subsets of glutamatergic synapses at multiple locations, including the prefrontal cortex (PFC), hippocampus, and nucleus accumbens (NAc), leading to a dysfunction of corticomesolimbic reward circuitry that underlies many of the symptoms of depression. This hypothesis accounts for current depression treatments and suggests an updated framework for the development of better therapeutic compounds.

Major depressive disorder: from a symptom-based description to biological phenotypes

Major depressive disorder (MDD) is one of the most common and costly of neuropsychiatric syndromes, with a lifetime prevalence of 7–12% in men and 20–25% in women, and a multibillion-dollar annual economic burden in the USA [1,2].

The most tragic consequence of untreated depression is suicide, attempted by as many as 8% of severely depressed patients. According to the Centers for Disease Control and Prevention, nearly half a million patients receive emergency care for suicide attempts each year in the USA and over 38 000 individuals die by intentional self-inflicted injuries, twice as many lives as are lost to homicide. Shockingly, 23% of suicide victims were being treated with antidepressants at the time [3]. In fact, only half of patients with major depression respond to standard-of-care antidepressants (ADs), such as selective serotonin reuptake inhibitors (SSRIs) [4], with 70% failing to achieve full remission [5]. A better understanding of the nature of the changes in the brain driving the range of behavioral symptoms that characterize depression is essential for developing more effective treatments for this disorder and preventing suicide.

In the search for ways to prevent, treat, and cure diseases, a strong hypothesis can prove invaluable if it accounts for known etiologies, is consistent with existing human and preclinical data gathered across a range of modalities, makes clearly testable predictions, explains the effectiveness of existing therapies mechanistically, and offers guidance for the development of novel prophylactic and

Glossary

Allostatic load/overload: allostasis is the concept that homeostatic set-points can be differentially regulated to meet different demands in the internal and external environment (e.g., physical or psychological stress). Repeated allostatic adaptation exacts a cost on the brain.
Chronic restraint stress: animals are placed in restraint tubes for several hours daily, repeated over several days (e.g., 4 hours/day for 10–14 days).
Chronic social defeat: animals are typically placed in the home cage of a novel aggressor for 30 min, once daily for 3 weeks.
Chronic unpredictable stress: animals experience two bouts of one of many mild stressors twice per day for 3 weeks.
Forced swim test: animals are placed in a tank of water until they cease struggling. Naïve, unstressed animals have longer latencies to cease struggling compared with stressed animals.
Learned helplessness: animals receive a single session with repeated unpredictable and uncontrollable stressors (foot shocks).
Learned helplessness test: animals are placed in a chamber where they previously received inescapable foot shocks paired with a conditioned stimulus. Latency to escape from the same chamber is later measured in response to the conditioned stimulus.
Novelty suppressed feeding test: animals are food deprived then placed in a brightly lit arena with food in the center. The latency until they venture into the center and eat is measured. Naïve, unstressed animals display a shorter latency compared with stressed animals. This test may reveal more about anxiety than about hedonic state.
Social interaction test: animals are placed in an arena with a novel juvenile animal held in a small cage. Time spent in the vicinity of the cage is compared in the presence and absence of the juvenile. Naïve, unstressed animals spend more time in the vicinity of the cage when the juvenile is present, whereas chronically stressed animals do not, presumably because the social interaction is no longer rewarding.
Sucrose preference test: a two-bottle choice between plain water and dilute (1%) sucrose solution. Naïve, unstressed animals drink approximately 80–90% of their liquid from the sucrose solution, whereas chronically stressed animals drink nearly equally from both bottles, presumably because the sucrose solution is no longer rewarding.
Tail suspension test: mice are dangled by their tails until they cease to struggle. Naïve, unstressed animals have longer latencies to immobility compared with stressed animals.

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therapeutic approaches. The serotonin hypothesis of depression, formulated during the early 1960s, provides an excellent example, driving the field of biological psychiatry forward and leading to the development of SSRIs (Box 1). More recently, considerable evidence of the involvement of neurotrophins in depression and antidepressant action has accumulated, leading to a neurotrophin hypothesis of depression (Box 2). Nevertheless, these hypotheses leave many questions about both the causes and treatment of depression.

In this review, we highlight emerging evidence of dysfunctions of excitatory synaptic transmission [6], and suggest how this defect correlates with the genesis of depression and the evidence that serotonin and neurotrophins have a role in depression. We are now moving beyond a symptom-based description of depression as a single disease entity and beginning to identify biological phenotypes that can be compared across species and across classically defined labels, as encouraged by the Research Domain Criteria of the National Institute of Mental Health (NIMH). Thus, a significant goal of basic research is to identify the neurobiological consequences of disease-promoting conditions at the level of alterations in gene products, synapses, cells, and circuits, and then, in a bottom-up manner, map these discoveries to the specific behavioral deficits characterizing human neuropsychiatric conditions. Here, we focus on the circuits mediating reward behavior, which underlies many of the symptoms of human depression, such as anhedonia and aberrant reward-associated perception and memory. We also highlight how this excitatory synapse hypothesis of depression offers a new framework with which to approach the treatment of patients with depression.

The etiology of depression

Despite its high incidence and its socioeconomic impact, the causes of depression remain poorly understood. Depression involves a combination of genetic and epigenetic susceptibility together with environmental risk factors, such as stress, emotional trauma, or traumatic head injury [7], with heritable factors contributing slightly less than half of the risk. Many SNPs and epigenetic differences are linked to increased risk for depression, but no single gene candidate produces a strong enough effect to provide convincing mechanistic hypotheses [8]. This reinforces the fact that MDD is a complex and heterogeneous collection of symptoms caused by variations in multiple genes, each responsible for a small effect on risk, that ultimately converge onto common circuit, cellular, and molecular pathways.

Stress and depression

Stressful life events are a key environmental risk factor for depressive disorders in genetically susceptible individuals [9] and are suspected to be causal in many patients. Patients who are depressed report more stressful life events and have fewer social resources compared with nondepressed subjects [10]. Personality traits, in particular neuroticism and lack of a confidence, have also been linked to the etiology of depression and may increase risk in response to stress [11].

McEwen, Sapolsky, and others emphasized the importance of allostatic overload (see Glossary) as an explanation for many chronic illnesses of modern human life, including depression [12,13]. These stressors may be physical or psychosocial, the latter including low self-esteem, loneliness, deficient social skills, excessive anxiety, rumination, and negative thinking. All stressors activate the sympathetic nervous system and the hypothalamus–pituitary–adrenal (HPA) axis, causing elevation of glucocorticoids (GC) and other stress hormones. Normally, the physiological stress response is self-terminating, due to negative feedback, directly via the hypothalamus and pituitary and indirectly via several brain

Box 1. The serotonin hypothesis of depression

The monoamine neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) is synthesized by neurons in the DR nucleus. These neurons integrate inputs from multiple brain regions, including the NAc, amygdala, LHb, and PFC, and send projections throughout the brain, including to the hippocampus, PFC, substantia nigra, and NAc.

Chance observations of mood-altering compounds more than 50 years ago led to the first coherent theory of depression and opened the door for current first-line treatments. Evidence that these agents alter the concentration of monoamine neurotransmitters, such as serotonin, dopamine, and norepinephrine (e.g., [136]), led to the hypothesis that depression is caused by a deficiency of monoamines [137–139]. Given that the pharmacological profile of many AD drugs is more consistent with changes in serotonin levels than of other monoamine neurotransmitters, it is now more common to speak of a serotonin hypothesis of depression, although inhibitors of norepinephrine uptake are also effective ADs, including the tricyclics. Most statements of the serotonin hypothesis fail to offer mechanistic explanations; nevertheless, this theory became a foundation for research in biological psychiatry, and the central dogma in the field of major depression for many decades.

Although deficits in serotonin levels or release are a central prediction of this hypothesis, the relation between human depression and the levels of serotonin or its metabolite 5-hydroxyindoleacetic acid (5-HIAA) remains unclear, with early enthusiasm giving way to mixed results [140]. Experimental manipulations of serotonin levels in humans by depleting or enhancing the precursor for its synthesis, tryptophan, also remain inconclusive [141–144]. In general, acute manipulation of tryptophan levels is more likely to affect mood in patients who are depressed than in otherwise healthy individuals, perhaps because it impairs the beneficial actions of their SSRIs.

One prediction of this hypothesis is that elevation of serotonin levels would relieve the symptoms of depression, and testing this prediction led directly to the development of SSRIs, which produce a rapid elevation of extracellular serotonin concentration [145]. With fewer adverse effects than the less-specific tricyclics, SSRIs were prescribed to tens of millions during their first decade.

SSRI-induced elevation of serotonin increases activation of serotonin receptors, of which there are 14 subtypes, each having a unique pattern of expression and localization. Alterations in a single population, or subpopulation, of serotonin receptors might also be responsible for the symptoms of depression, rather than a global dysfunction of the neurotransmitter system, but evidence of such changes remains inconclusive [146–148].

Fifty years after the initial observations, considerable debate about the validity of the serotonin hypothesis remains, with only inconsistent and inconclusive evidence supporting it. It is unlikely that depression is caused by a simple decrease in serotonin synthesis, release, or receptor expression. Nevertheless, there is clear evidence that elevated levels of monoamines can relieve the symptoms of depression.